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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,252	07/25/2001	Ed Croze	BERLX-79	4123

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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 10/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/912,252	CROZE ET AL.	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28-40 and 42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-40 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment filed on 8/1/05 has been entered.

Amended claims 28-40 and new claim 42 are pending in the present application, and they are examined on the merits herein.

Response to Amendment

The New Matter rejection is withdrawn in light of Applicant's amendment.

The rejection under 35 U.S.C. 112, first paragraph, is withdrawn for amended claims 28-41 in light of Applicant's amendment.

Claim Objections

Claim 42 is objected to because of the lack of the article - - a - - in front of the term "human IFNAR2c" on line 5 of the claim. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New claim 42 is rejected under 35 U.S.C. 112, first paragraph, because while being enabling for:

A method of increasing the inhibition of cellular proliferation in human tumor cells, when said tumor cells are contacted with a human type I IFN and wherein said tumor

cells possess functional interferon alpha receptor 2c (IFNAR2c) polypeptide chains, said method comprises the steps of: using electroporation to introduce directly into said tumor cells an exogenous gene encoding a human IFNAR2c polypeptide chain to form modified tumor cells with an increased number of functional IFNAR2c polypeptide chains and contacting the modified tumor cells with a therapeutically effective amount of a human type I IFN, and thereby increasing the inhibition of cellular proliferation in the modified tumor cells;

does not reasonably provide enablement for a method of increasing inhibition of cell proliferation in any other human target cell population and/or by introducing into cells of any human target cell population an exogenous gene encoding a human IFNAR2c polypeptide by any route of delivery using electroporation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims for the same reasons already set forth in the previous Office Action mailed on 5/17/05 (pages 4-10).

The examiner notes that new claim 42 has the same enablement issues that were raised in the previous Office Action mailed on 5/17/05, and yet Applicant's amendment filed on 8/1/05 failed to address any of these issues (see page 5).

Amended claims 28-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter

which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make **and/or use** the invention. ***This is a new ground of rejection.***

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The specification teaches by exemplification showing that various human tumor cell lines (HT1080 cells, U5A cells, MDA231 cells) exhibit **enhanced sensitivity** to the antiproliferative effects (including apoptosis) of IFNβ1b or IFNα upon transfection with a human IFNAR2c gene. Applicants further demonstrated that LOX human melanoma cells transfected with a human IFNAR2c gene are also **more sensitive** to the *in vivo* anti-growth activity of IFNβ1b than the parental LOX cells. The above evidence has been noted and considered. However, the instant specification is not enabled for the method as claimed for the reasons discussed below. Please note that enablement requires the specification to teach how to make and/or **USE** the claimed invention.

(1) The breadth of the claims

The instant claims encompass a method of increasing the inhibition of cell proliferation in any human target cell population, when said cell population is contacted with a human type I interferon, wherein said target cell population possesses functional

IFNAR2c polypeptide chains, said method comprising the steps of increasing *in vitro* the number of functional human IFNAR2c receptor chains on the surface of cells within the target cell population to produce modified target cells by any means including the introduction of an exogenous gene encoding a human IFNAR2c polypeptide into the cells, and contacting the modified cells with a therapeutically effective amount of a human type I IFN.

(2) The state of the prior art

At the effective filing date of the present application (7/26/00), little was known on enhancing the inhibition of cell proliferation in any human target cell population already possessing functional IFNAR2c polypeptide chains and in contact with a human type I IFN by increasing the number of functional human IFNAR2c polypeptide chains on the surface of cells within the target cell population by any means, including the use of an exogenous gene encoding a human IFNAR2c polypeptide as evidenced by the teachings of Johns et al. (U.S. Patent No. 5,681,558; Cited previously), Domanski et al. (J. Biol. Chem. 273:3144-3147, 1998; Cited previously), Platanias et al. (J. Biol. Chem. 273:5577-5581, 1998), and Chen et al. (U.S. Patent No. 6,569,420; Cited previously). Additionally, even several years after the effective filing date of the present application and on the basis of the same set of data presented in the instant specification Applicants still state "It should be noted, however, that our current study utilized only immortalized cultured cells and **it is possible** that enhanced expression of IFNAR2c on **a primary non-cancerous cell may likewise sensitize them to the effects of IFN**. Unlike the cancer cell lines analyzed in our current study, **it is not known if IFNAR2c**

expression is rate limiting in primary non-cancerous cells. Therefore, clinically, it may be necessary to specifically deliver the IFNAR2c gene to a metastasized cancer cell or solid tumor *in vivo*" (page 41, right hand column, first paragraph, Int. J. Cancer 111:32-42, 2004; IDS).

(3) The amount of direction or guidance provided

When read in light of the specification, the sole purpose for a method of increasing the inhibition of cell proliferation in a human target cell population already possessing functional IFNAR2c polypeptide chains when said cell population is contacted with a human type IFN is for treatment purposes, particularly with the use of a therapeutically effective amount of a human type I IFN (see at least page 6, line 20 continues to line 5 of page 10). With respect to the method as claimed, the instant specification fails to teach a skilled artisan on **how to use** any target cells that have been modified *in vitro* by any means for increasing the number of functional human IFNAR2c polypeptide chains and being contacted with a therapeutically effective amount of a human type I IFN. It is unclear what is the use for making the type I IFN-treated and *in vitro* modified cells of a human target cell population that have increasing inhibition of cellular proliferation compared to non-modified cells? Please note that enablement requires the specification to teach how to make and/or **USE** the claimed invention.

With respect to the breadth of the claims, apart from the exemplification showing that the increased exogenous expression of functional IFNAR2c receptor polypeptides in various transfected human cancer cell lines; some of which possess functional

IFNAR2c polypeptide chains, resulted in enhanced sensitivity of the transfected cells to the antiproliferative effects (including enhanced apoptosis) of IFNβ1b or IFNα, the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain a similar enhanced antipoliferative activity of a type I interferon on any other human target cell populations. Despite the ability of all type I interferons to bind to the same type I interferon receptor, it should be noted that differences in signaling and biological effects exist among them as well as the cell types on which the interferons act on (Domanski et al., J. Biol. Chem. 273:3144-3147, 1998; Platanias et al., J. Biol. Chem. 273:5577-5581, 1998). Several years after the effective filing date of the present application the same Applicants still state "Unlike the cancer cell lines analyzed in our current study, **it is not known if IFNAR2c expression is rate limiting in primary non-cancerous cells**" (page 41, right hand column, first paragraph, Int. J. Cancer 111:32-42, 2004; IDS). Therefore, it is not clear that the increase in an exogenous expression of a human IFNAR2c receptor in any human target cell population would necessarily potentiate an inhibitory cell proliferation activity of a type I IFN. Since the prior art at the effective filing date of the present disclosure does not provide such guidance, it is incumbent upon the instant specification to do so.

Furthermore, apart from the exemplification showing increasing the number of functional human IFNAR2c polypeptide chains on the surface of cancer cells *in vitro* by introducing an exogenous gene encoding a human IFNAR2c polypeptide into the cells, the present application fails to provide any specific guidance for a skilled artisan on any other means for increasing the number of functional human IFNAR2c polypeptide

chains on the surface of cells within any human target cell population. For example, which other agents, such as which specific small molecule and/or which specific effector used under which exact conditions for increasing the number of functional human IFNAR2c polypeptide chains in targeted cells?

In light of the state of the art and given the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and/or **use** the method as claimed.

(4) Working example provided

The specification fails to provide an example showing an enhanced antiproliferative effect of a type I IFN has been achieved for any non-cancerous human target cell population apart from exemplified tumor cell lines. The instant disclosure also fails to provide an example demonstrating any other means apart from the step of introducing an exogenous gene encoding a human IFNAR2c polypeptide in human cancer cell lines for increasing the number of functional human IFNAR2c polypepide chains on the surface of targeted cells.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and/or use the method as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-40 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection.***

In claim 28, its dependent claims and claim 42, there is a lack of a nexus between the reciting steps (a) and (b) to the preamble of the claims. Therefore, the metes and bounds of the claims are not clearly determined. Clarification is requested.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's primary, Qian Celine, Ph.D., may be reached at (571) 272-0777, or SPE, Dave Nguyen, at (571) 272-0731.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D
PATENT EXAMINER